REVIEW ARTICLE

Treatment Algorithms for Chronic Osteomyelitis

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SUMMARY

Background: Osteomyelitis was described many years ago but is still incompletely understood. Its exogenously acquired form is likely to become more common as the population ages. We discuss biofilm formation as a clinically relevant pathophysiological model and present current recommendations for the treatment of osteomyelitis.

Methods: We selectively searched the PubMed and Cochrane databases for articles on the treatment of chronic osteomyelitis with local and systemic antibiotics and with surgery. The biofilm hypothesis is discussed in the light of the current literature.

Results: There is still no consensus on either the definition of osteomyelitis or the criteria for its diagnosis. Most of the published studies cannot be compared with one another, and there is a lack of scientific evidence to guide treatment. The therapeutic recommendations are, therefore, based on the findings of individual studies and on current textbooks. There are two approaches to treatment, with either curative or palliative intent; surgery is now the most important treatment modality in both. In addition to surgery, antibiotics must also be given, with the choice of agent determined by the sensitivity spectrum of the pathogen.

Conclusion: Surgery combined with anti-infective chemotherapy leads to long-lasting containment of infection in 70% to 90% of cases. Suitable drugs are not yet available for the eradication of biofilm-producing bacteria.

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Infectious diseases of the skeleton have been known from the earliest stages of human development. Signs of burned-out osteomyelitis have been found in hominid fossils (*Australopithecus africanus*), and the symptoms are described in the oldest medical texts (Edwin Smith papyrus) (1–3).

Despite this, it has to this day proved impossible to identify definite criteria that would allow a reliable diagnosis. It is therefore very difficult to compare different investigation and treatment methods, and evidence-based results are few. The reason for this is the most important characteristic of the disease: the extreme variety of symptoms that can be manifested in chronic osteomyelitis. This variety makes a systematic description difficult; even experienced clinicians are repeatedly taken by surprise by new and unpredictable courses of the disease (4–6).

The clinical picture of chronic osteomyelitis has changed markedly in the past 70 years. With the arrival of antibiotics, it seemed at first to have lost its ability to inspire fear. In the industrialized countries, hematogenous osteomyelitis has been almost completely wiped out (7).

The acquired post-traumatic/postoperative form, on the other hand, is on the increase. Because of the changing age structure of the population and the increasing number of surgical and orthopedic implantations, a further rise is expected in the near future (8, 9). For this reason, a review and explanation of current treatment concepts seems appropriate.

Methods

A literature search on treatment algorithms for chronic osteomyelitis was carried out in PubMed and the Cochrane Library. For German-language publications, we searched the databanks of the publishers Springer-Verlag and Thieme-Verlag and in current textbooks on septic surgery.

To date, the Cochrane Library contains one review on the medical treatment of chronic osteomyelitis (10).

A search of the PubMed library using the search term (“chronic osteomyelitis” OR “bone infection” OR “chronic osteitis”) and therapy) AND systematic[sb] identified 15 reviews. Eight publications appeared relevant to the topic and were evaluated (10–17). We were looking for local and systemic antibiotics and surgical procedures used to treat chronic osteomyelitis. The biofilm theory is explained on the basis of current literature.

BOX

Risk factors in wound and bone healing (adapted from [e34])

- Systemic risk factors
 - Malnutrition
 - Kidney or liver failure
 - Diabetes mellitus
 - Respiratory failure
 - Immune deficiency (e.g., AIDS, granulocyte deficiency, complement deficiency)
 - Malignant tumor
 - Very young or very old age
 - Nicotine abuse
 - Immune suppression (e.g., chemotherapy, transplantation)
- Local risk factors
 - Chronic lymphedema
 - Chronic venous insufficiency
 - Macroangiopathy
 - Extensive scarring
 - Radiation fibrosis
 - Small-vessel vasculitis
 - Neuropathy

Epidemiology

Treatment-refractory acute infectious complications were the most frequent cause of chronic osteomyelitis in the developed countries (18). In elective trauma surgery, these occurred at a rate of 1% to 5% after closed fractures and—depending on severity—in 3% to 50% after first- to third-degree open fractures (19). Overall, infectious complications occur in 5% of traumatic/orthopedic implants during the lifetime of the implant (20).

In primary hip and knee replacements, early infections are expected in 0.5% to 2% of cases. In aseptic revision operations, deep infections occur in 5% of cases; after “septic” revisions, the rate rises to more than 20% (21).

In 10% to 30% of patients, acute osteitis becomes chronic (18).

Definition

The term “osteomyelitis” refers to infection of the bone marrow; the term “osteitis” describes involvement of the entire organ including the bone cortex. In the Anglo-American world, “osteomyelitis” is the preferred term and is synonymously used for both conditions.

There is at present no generally accepted, interdisciplinary classification of osteomyelitis (6, 7, 18, 22).

In clinical practice it is useful to distinguish between an endogenous and an exogenous form. The former is caused by hematogenous spread of a focus distant from the manifestation, usually monomicrobial, and makes up around 20% of cases (7, 23). It is primarily treated conservatively (23, 24).

In the exogenous form, the pathogen is inoculated directly, by trauma or intervention, and therefore is often polymicrobial. First-line treatment is surgical (7).

This classification stems from a suggestion by Lew and Waldvogel, who also distinguished a third, ischemic form (25). It is most frequently found in the diabetic foot and, in our experience, once the perfusion of the foot has been improved its course is fundamentally no different from that of exogenous osteitis.

An acute infection usually becomes manifest during the first 2 weeks after inoculation with the pathogen. Chronic osteomyelitis becomes symptomatic several weeks to months after infection. It is not possible to define a time threshold after which an acute infection becomes chronic, but the two forms may be distinguished by the fact that dead bone tissue and host reparative reactions (involucrum [Glossary]) are only found in the chronic form (7).

Pathophysiology

In industrialized countries, post-traumatic and post-operative osteitis is by far the most important form, accounting for 80% of bone infections. Around 10% to 30% of cases of the acute form become chronic (18). Local and systemic risk factors have a predisposing effect (Box) (e1, e2).

Figure 1:
a, b) A 39-year-old woman with a 20-year history of chronic recurrent femoral osteitis, who had undergone five revisions. Deformation, sclerosis, iatrogenic defects after marrow revision, PMMA beads placed
c) MRI (STIR sequence) shows deformation of the right distal femur and marked signal inhomogeneity of the bone, with increased signal in some parts and marked signal decrease where the beads were placed. Adjacent faint lamellar periosteal fluid collections

Chronic osteomyelitis is difficult to treat and is characterized by frequent relapses. It manifests itself when an imbalance occurs between the virulence and quantity of inoculated bacteria on the one hand and the host's defenses on the other (e3). Our understanding of the pathophysiology has been greatly improved by the biofilm model, which explains the wide variety of symptoms and the changeable course.

The conditions required for a biofilm (*Glossary*) to form are necrotic tissue and bone, which have a foreign-body effect and are colonized by bacteria. The pathogens first form surface colonies, which then multiply into a three-dimensional structure. They communicate via chemical signals that function as autoinducers, allowing coordinated behavior both within and between species ("quorum sensing" [*Glossary*]) (e4, e5). This matrix offers the bacteria protection from mechanical influences and makes it harder for antibiotics, the body's own defense cells, and antibodies to penetrate, functioning as a diffusion barrier. The pathogens pass from a planktonic phase (*Glossary*) with a high metabolic rate and rapid multiplication into a sessile form (*Glossary*) with greatly reduced metabolism and slowed biological reactions. This can reduce their sensitivity to antibiotics by a factor of 10^3 (e6).

The body's own defense system is inhibited by a sequester (*Glossary*) in the same way as by the implant in a foreign-body-associated infection. Neutrophilic

granulocytes penetrate the biofilm poorly and in the process lose their ability to phagocytose. Apoptosis occurs with excessive complement activation and release of radicals and proteases, resulting in a local immune deficiency.

In the lower layers of the biofilm, conditions are anaerobic, massively reducing the growth rate and metabolic activity of the pathogens. So-called "persisters," metabolically inactive pathogen populations, are largely insensitive to antibiotics. After treatment has ended, they can return to an active mode and then show resistance to the originally administered anti-infectives (e7).

A return from the sessile to the planktonic phase is possible, and clinically this can trigger local or systemic recurrence of the infection. The biofilm population thus functions as a permanent source of virulent pathogens that themselves are insensitive to the body's own immune system and to administered antibiotics. The safest treatment at present, therefore, is surgical removal of the sequestrum that bears the biofilm (5).

This very simplified model has still to be documented in detail by in vivo studies. Many of the processes governing the formation of the biofilm are still not understood. However, it represents the best model so far of the clinical picture of a chronically recurrent disease, and indicates some starting points for a reasonable therapy (e6, e8–e12).

FIGURE 2

Treatment options for chronic osteomyelitis

Another cause of chronic infections are slow-growing pathogens, which form what are known as “small colony variants” (SCV) and are difficult to culture. They can penetrate cells unable to phagocytose, and can survive intracellularly, insensitive to currently available antibiotics (e13, e14).

Causative pathogens

In around 75% of cases of chronic osteomyelitis, the causative pathogens are *Staphylococcus aureus* and coagulase-negative staphylococci. In reducing order of frequency, and depending on individual patient disposition, streptococci, gram-negative pathogens (enterobacteria, pseudomonads), and anaerobic bacteria have been demonstrated; rarely, mycobacteria and fungi are found. What they all have in common is the ability to form a biofilm (5, 7, 25, e2).

Diagnosis

At present no uniform clinical definition of chronic osteomyelitis exists, so many authors define their own criteria. This makes it impossible to compare different approaches to examination and treatment (6).

A diagnosis of chronic osteomyelitis becomes more probable, the more points are gained on a score that includes clinical, laboratory, imaging, microbiological, and pathohistological features. For more details, see the recent publication by Schmidt et al., which reports a detailed evaluation of findings (6).

A history and clinical examination will provide important clues to the diagnosis. In many cases the symptoms of chronic osteitis are discreet and the classical signs of infection are absent. In patients who are very old, immune suppressed, or who have a polyneuropathy, often only one or a few symptoms are found (6). Relatively often, patients will report recurrent dull pain; a fistula to bone weeping pus is

pathognomonic. Late sequelae are implant loosening, implant failure, pathological fracture, and—rarely—fistular carcinoma (18). Serum infection markers can be within the normal range (e15).

The basic diagnostic procedure requires a detailed history and clinical examination, laboratory tests (blood values, C-reactive protein), and X-rays in two planes. The radiologic appearance is characteristically variegated with osteolysis and destruction with sclerotic zones and periosteal bone appositions (6) (Figure 1). Further investigation is by contrast magnetic resonance imaging, unless contraindicated (e16). Before antibiotic therapy is started, deep tissue samples should be taken for microbiologic examination (22).

Treatment

Surgery

To date, no evidence-based guidelines exist on the treatment of chronic osteomyelitis. Basically, the choice is between a palliative and a curative approach. A decision must therefore be made on an interdisciplinary basis as to what treatment the patient can tolerate (Figure 2). The patient’s quality of life must not be reduced by the treatment, but improved. Radical segmental resections (*Glossary*), explantation of hip and knee prostheses, and major amputations are stressful operations that can carry high risks despite optimal anesthesia and the most sparing operative technique (21, e17).

The curative approach to chronic osteomyelitis has the following goals:

- Arrest the infection
- Reduce pain
- Retain limb and function.

If treatment fails, there is a risk of local and systemic recurrence of infection which may lead to sepsis and multiorgan failure. Dependence on or abuse of painkillers can destroy both private and working life. Very old patients are often unable to compensate for the loss of a limb and become dependent on care.

If a curative approach is chosen, radical surgical resection including healthy bone and soft tissue is required, as in an “oncologic approach” (4, e18). All foreign bodies, including broken-off screws, reamers, cerclages, and cement remains are removed, as are all implants that might be biofilm carriers. An infected marrow should be reamed out and irrigated if possible in order to remove necrotic, infected tissue from the medullary cavity (e19). The resected edges must be so viable and well-perfused that they can accept a transplant or consolidate at the docking site. There are no objective criteria for defining the resection limits; that remains the individual decision of the surgeon concerned (e20).

The procedure is divided into four steps (e21):

- Radical sequestrectomy
- Dead space management
- Soft tissue reconstruction
- Restoration of bone stability.

Figure 3 a–d: A 75-year-old man with acute recurrence of chronic post-traumatic femoral osteitis which had been dormant for 17 years. Necrotizing soft tissue infections with evidence of methicillin-resistant staphylococci (MRSA) and hemolytic group G streptococci. On admission he had a 5-day history of progressive pain in the right distal thigh, leukocytes were $19\,600/\text{mm}^3$, C-reactive protein 31 mg/dL (norm $<0.5\text{ mg/dL}$). Radical débridement with excision of skin, fascia, and parts of the left distal vastus lateralis, wide femoral resection, bone marrow revision and reaming, temporary wound closure with artificial skin. Staged revision after 48 hours with knee joint revision, subtotal synovectomy, implantation of gentamicin–Palacos spacers. Later, débridement with joint irrigation, placement of PMMA beads, and a total of six further revisions. Local flap graft using the biceps femoris and a myocutaneous lateral gastrocnemius flap. This was followed by long-lasting remission. Five months later the patient suffered a pathological fracture on twisting his knee. He was treated with an external fixator and cancellous bone graft. Full weight bearing possible after 6 months, follow-up after 12 months

GLOSSARY

- **Biofilm**
A coherent cluster of bacterial cells imbedded in a matrix—which are more tolerant to most antimicrobials and the host defence than planktonic bacterial cells.
- **BMP**
Bone morphogenetic protein, signaling molecules, cytokines of the transforming growth factor beta signal path. BMP-2 and BMP-7 are manufactured industrially, stimulate—among other things—osteoblasts, and are licensed for certain indications for promotion of bone growth. Cost intensive.
- **Half-/partial segmental bone resection**
Half- or partial-thickness removal of bone. It is usually possible to retain some bone stability, so that filling of the defect with a cancellous bone graft is sufficient for bone consolidation. Additional osteosynthesis is required only exceptionally.
- **Involucrum**
(Latin: cover, wrapping) Reactive formation of new bone around an infection focus/ sequestrum or abscess.
- **Planktonic phase**
Free-floating bacteria, virulent, reproductive, triggering host reactions, sensitive to antibiotics, may be cultured. Contain <0.1% of the bacteria in the ecosystem (e35).
- **Sessile phase**
Bacterial population living in a slime layer, communicating via signaling molecules. Low metabolic activity, restricted reproduction, difficult to culture, tolerant to antibiotics and immune defenses (e35).
- **PMMA**
Polymethylmethacrylate, bone cement used to affix implants. As PMMA beads, can be impregnated with gentamicin at various dosages, e.g., 30 beads of 7 mm diameter and 7.5 mg gentamicin sulfate. Used for local antibiotic therapy and bone remodeling. Produced industrially.
- **Quorum sensing**
Communication circuits that operate between and within bacterial species and regulate metabolic processes in response to fluctuations in cell-population density, via signaling molecules. Enables reaction to changing environmental situations, thus giving an important selection advantage (e4).
- **Segmental bone resection**
Full-thickness removal of bone. Leaves an unstable defect that can only be treated by shortening/interposition plus osteosynthesis or callus distraction.
- **Sequestrum**
Fragment of dead bone, potential carrier of bacteria and biofilm.

The size of the defect produced by the procedure is not a primary consideration; only the vascular and nerve supply should be preserved. What happens next depends on how radical the débridement and resection was. The important thing is management of the dead space, which if not treated properly may lead to early recurrence of infection. Implantation of PMMA beads (*Glossary*) on the bone has been used successfully; Palacos spacers with or without added antibiotics are also suitable.

As a temporary replacement for soft tissue, vacuum occlusion may be used to condition the transplant site. If clinical examination and blood tests show the infection to have been arrested, definitive soft tissue closure is carried out 6–8 days later using a local free fasciocutaneous or free muscle flap. Once this has healed, the right conditions have been created for definitive stabilization. For segmental defects longer than 3 or 4 cm, callus distraction using the Ilizarov technique or a vascularized pedicled bone graft is carried out (e22–e24). It is possible that in future the use of bone morphogenetic proteins (BMPs) (*Glossary*) will facilitate bone reconstruction (e25). In smaller or half-segmental defects (*Glossary*), autologous cancellous bone graft is often sufficient (*Figure 3a–d*) (e26).

Interdisciplinary treatment with close collaboration between trauma surgeons/orthopedists, plastic surgeons, radiologists, microbiologists, and anesthetists is essential for successful management of chronic osteomyelitis. Often vascular surgeons and internal medicine specialists need to be called in as well. During the critical phases of treatment, close monitoring by the responsible surgeon is required, and he or she should also either perform all treatment interventions him or herself, or be present when they are performed. This continuity of care is best ensured in facilities that have been staffed and funded to deal with complex and resource-heavy treatment. When this is the case, success rates are between 70% and 95% (e19).

If the infection can be arrested and the patient stabilized for the long term, usually no ongoing medication is required. Nevertheless, the term used is not “healing” of an infection, but “remission” or “arrest” (7).

If the patient’s general condition does not permit extensive interventions, palliative treatment should be undertaken if possible, with the aim of controlling the infection and relieving pain. Available measures are bone marrow trepanation, local sequestrectomy, soft tissue revision, and permanent drainage (e27).

Additional measures are proper, systemic antibiotic therapy, preferably oral, and sufficient pain treatment. Often long-term medical treatment, with its ensuing physical and economic consequences for the patient and the community respectively, is unavoidable. If the infection focus cannot be removed, periodic exacerbations and a progressive course must be expected.

Medical therapy

If a curative approach is chosen, surgery is the most important element at present, and is likely to remain so for the foreseeable future. Surgery alone is not enough, however; it requires supportive antibiotic treatment. Various treatment regimes have been suggested, none of which has so far proved superior to any other. Empirical therapy starts after deep tissue samples have been taken for microbiological analysis and is directed against the expected pathogen spectrum. Beta-lactam antibiotics are used; they are usually well tolerated and achieve high enough effective serum concentrations (e28).

Alternatively, lincosamides and gyrase inhibitors may be given. There is debate about the value of combination therapy, which to date has mainly been used in patients with implant-related and perioperative infections (e29, e30). Some support its use in treating infections with problem pathogens (e31, e32). So far no evidence-based advantages have been identified (7, e33).

Opinions also vary about the duration of treatment. The younger the patient, the shorter the antibiotic treatment (14). Children are usually treated for 2 weeks, adults for 4 to 6 weeks. Once the antibiogram (based on bone biopsy cultures) is received, empirical therapy is replaced by targeted anti-infective therapy. The procedure is based on animal studies and on the knowledge that revascularization of an adult's bone requires 3 to 4 weeks. To what extent this approach is valid for the reality of osteolytic human bone, and whether these treatment durations are really required, is not known (13). The literature search identified no studies that were able to show statistical evidence of the advantages of any particular medication. Likewise, the effectiveness of local antibiotic therapy has not been scientifically proven (e33).

Prevention

The most effective way to prevent acute post-traumatic osteomyelitis is by careful, appropriate, timely care of the injured bone and soft tissue (4, 19, e32). Overcoming the acute infection is the best prophylaxis against a chronic course (18). At present it looks as though reducing the infection rate below the 1% to 2% achieved in elective trauma surgery and orthopedics—a level that has remained stable for years—will not be possible. Current efforts are therefore directed at providing a coating on implants to prevent pathogen adherence. Another approach is investigating stimulation of the immune system against staphylococcal antigens (for review see [5]). At present these procedures are not available under standard health care provision.

Conflict of interest statement

The authors declare that no conflict of interest exists.

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KEY MESSAGES

- Two forms of chronic osteomyelitis are distinguished, the one endogenous/hematogenous, the other acquired through direct contact. The latter represents about 80% of cases of chronic osteomyelitis in the industrialized countries.
- Chronic osteomyelitis has a multifactorial origin, so interdisciplinary collaboration is required for treatment to be successful.
- At present there is no single accepted definition of the disease, and therefore there are no evidence-based studies on its treatment.
- A choice must be made between a curative or a palliative approach to treatment, depending on the patient's co-morbidities. The goals of treatment are long-lasting arrest of the infection, pain reduction, and restoration of function.
- Surgical débridement is critical to the success of treatment in post-traumatic/postinterventional osteomyelitis. In specialized centers, infection arrest is achieved in 70% to 95% of cases.

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